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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/374,213	08/13/99	STERN	D 59472/JPW/SH

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EXAMINER	
WEGERT,S	
ART UNIT	**PAPER NUMBER**
1647	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/374,213	Applicant(s) STERN ET AL.	
	Examiner Sandra Wegert	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-33 and 41-58* is/are pending in the application.

4a) Of the above claim(s) *33,42,43,45 and 47-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-32,41,44,46 and 55-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claims *30-33 and 41-58* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 August 1999* is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The Information Disclosure Statement received 12/29/99 (Paper 4) has been entered into the record. Applicant's election of Invention II, (claims 27-33) in Paper No. 6 is acknowledged. In addition, Applicant elected the following species: A) a peptide capable of forming amyloid, B) sRAGE, and C) a mononuclear phagocyte. Claims 1-26 and 34-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Inventions, there being no allowable generic or linking claim. Additionally, Claims 27-29 were cancelled in Paper 6 and new claims were added numbering 41-58. It should be noted that claims will be examined insofar as they read on the elected Invention and Species. Claims 33, 42, 43, 45, and 47-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Inventions, there being no allowable generic or linking claim. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 30-32, 41, 44, 46, and 55-58 are under examination in the Instant Application.

Informalities

Specification

The disclosure is objected to because of the following informalities:

Figures

The drawings are objected to for reasons illustrated in Form PTO 948 (enclosed). Corrections will be required in the event any claims are allowable.

Claims

Claim 30 is objected to because it depends from claim 27, which was canceled.

Claims 45 and 55 are objected to because they recite or encompass non-elected inventions.

Appropriate correction is required.

Claim Rejections

Claim Rejections - 35 USC § 103, obviousness.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 41, 44, 46, 55 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yan, et al (PNAS, 1997, 94: 5296) in view of Hale, et al (Cytokine, 1995, 7: 26) and Heaney, et al (Blood, 1993, 82: 1945).

Yan et al teach that amyloid beta peptide binds to the receptor for RAGE. They also demonstrated that binding of amyloid to the RAGE receptor induces oxidative stress, activation of microglia, and activation of inflammatory pathways involving transcription factor NF-κB. They further suggest that these processes may contribute to the cellular pathologies seen in Alzheimer's Disease. They do not teach inhibition of this binding event.

Hale, et al, teach inhibition of tumor necrosis factor using the soluble form of its receptor. Elevated levels of TNF are significant in the pathology of sepsis and the circulatory collapse that can result from severe sepsis. Soluble receptors for TNF were shown to be effective in inhibiting the binding of TNFα to the cell-surface receptors. sTNFR's were also effective in inhibiting the effects of TNF in culture as well as in several models of sepsis in mice and baboons (p. 27 and 33). They further suggest that endogenous "soluble receptors may be part of a negative feedback mechanism to inhibit the biological effects of TNF".

In fact, Heaney and Golde give numerous examples in which soluble receptors are involved in intercellular signaling (p. 1946, for example). They discuss the consequences of such signaling to disease states, and suggest multiple roles for soluble receptors: for example, to temporarily inhibit or confer sensitivity to a ligand (p. 1947). They conclude their discussion by stating that "construction and development of soluble receptors as pharmaceuticals may be useful to specifically inhibit or facilitate hormone action in disease states."

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the soluble form of RAGE to inhibit binding of an amyloid peptide that is known to bind the membrane-bound form of RAGE. The teachings of Yan et al, demonstrated binding of β-amyloid to the

receptor for AGE on the surface of cells. Binding triggers a cascade of events that may be important in generating oxidative stress in cells expressing RAGE. An obvious way to inhibit such an event is to use the soluble form of the receptor to "out-compete" the endogenous binding. The literature gives examples of soluble receptors and examples wherein disease states have been successfully ameliorated using soluble receptors.

The person of ordinary skill in the art would have been motivated to try to inhibit such binding events as those in the instant application. He would have reasonably expected success using a soluble form of the receptor to "tie-up" ligand, because he knows from the literature that the ligand binds the receptor. Furthermore, there are examples in the literature where similar methods were used to bind ligand and thus affect the outcome of a disease triggered by a binding event.

35 *USC § 112, first paragraph - lack of enablement*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 30-32, and 57-58 are rejected under 35 U.S.C. 112, first paragraph, because the subject matter was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is not enabling for the limitations of the claims wherein a method of inhibiting binding of a peptide that forms amyloid to a membrane-bound receptor for AGE is described.

Claims 30-32, and 57-58 are drawn to a method of inhibiting binding of an amyloid peptide to a membrane-bound receptor for AGE. The specification discloses using the soluble form of the receptor to inhibit binding of amyloid to RAGE by concentration-dependent competition binding. Experiments were described in which inhibition of binding between amyloid and RAGE was measured in PC12 cells

transfected with RAGE. The disclosure also described applying sRAGE to mouse splenic cells and subsequently measuring the changes in amyloid formation and changes in NFκB and interleukins.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

A sufficient amount of direction or guidance is lacking in claims 30-32, and 57-58. The specification gives examples wherein binding of amyloid by sRAGE in splenic cells or RAGE - transfected PC12 cells is inhibited in culture. However, nowhere in the specification is a nexus described between inhibition of binding of amyloid and a disease state. The examples are directed to methods of inhibiting binding of an amyloid peptide to RAGE on cultured or isolated cells. Later transduction events *are* described and measured: specifically the subsequent increase in NFκB and interleukins after binding of amyloid to cells. However the relationship between these early events and disease is poorly understood. In addition, Alzheimer's disease therapy is highly unpredictable, and using the methods described to obtain *any* clinical effect would require a large amount of experimentation.

In summary, the specification does not provide a description of a repeatable process of inhibiting binding of an amyloid peptide to RAGE on cultured or isolated cells in such a way as to modulate a disease state involving "β-sheet fibrils" . In addition, the predictability of the art is very low with regard to the results of inhibiting binding of an amyloid peptide to RAGE in a mammal with a disease involving a "β-sheet fibril" in the manner specified. For this reason undue experimentation would be required to determine effective methods of inhibiting binding of an amyloid peptide to RAGE to ameliorate a disease state.

35 USC § 112, first paragraph - scope

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 41, 44, 46 and 55-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting binding of β-amyloid to RAGE *in vitro*, does not reasonably provide enablement for inhibiting binding of amyloid to RAGE *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to the use of soluble RAGE to inhibit binding of amyloid peptide to RAGE. The specification discloses methods for using the soluble receptor for AGE as an inhibitor of binding of a β-sheet fibril to the membrane-bound RAGE. The scope of the patent protection sought by the Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification for the following reasons:

The specification discloses an enabled utility for soluble RAGE as to be used to inhibit binding of amylin, β-amyloid or related peptides to the membrane-bound receptor for AGE in PC12 cells. The specification reads on a curative or preventative therapy for certain dementias such as Alzheimer's disease. However, Alzheimer's disease is a highly complex disorder that may take *years* to develop (Pearlman, et al. Neurobiology of Disease, pp 307-318, esp. pp 310-311). In addition, multiple neuronal cell types are involved (pp 315-317), and several protein types contribute to plaques and tangles (pp 316-317). Despite several lines of research ranging from genetics and immunology to pharmacology and cognitive sciences, and despite the fact that the clinical diagnosis is relatively unambiguous, at least in

later stages, Alzheimer's disease is still seen as a largely incurable and untreatable disease (pp. 310-313). Furthermore, there is no discussion in the instant application of how to administer sRAGE in humans and how to measure the clinical effects. There are no discussions of routes of administration, side effects, or dosages needed.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Due to the large quantity of experimentation required to determine how to use soluble RAGE to inhibit amyloidosis *in vivo*, the lack of direction or guidance in the specification regarding same (e.g., the lack of guidance regarding specific activity of sRAGE in humans), the lack of working examples to same, the state of the art showing the unpredictability of treating dementias, and the breadth of the claims which embrace *in vivo* methods, undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, second paragraph, indefiniteness.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 30, 31, 32, 41, 44, 46, 55, 56, 57, 58 are rejected under 35 U.S.C. 112, -second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims encompass a method of using sRAGE for preventing the interaction of an amyloid-forming peptide with RAGE. However, one skilled in the art cannot determine the metes and bounds of the claimed invention because there is no recognized structural or functional determinants in the claims such that the molecules encompassed can be distinguished from any other molecule. Aside from the art-recognized *names* of the molecules used for the claimed invention, there is nothing to distinguish them from similar peptides from other species, nor from mutants and variants.

Conclusion

Claims 30, 31, 32, 41, 44, 46, 55, 56, 57, 58 are rejected for the reasons cited above.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (703) 308-9346. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SLW

6/26/01

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER